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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/293,670
Filing Date: April 16, 1999
Appellant(s): FISHER ET AL.

James Keddie
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 5/7/08 appealing from the Office action mailed 08/10/07.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

This appeal involves claims 17-26, 30 and 32.

Claims 26(with respect to the non-elected species), 27-29, 31, 33-36 are withdrawn from consideration as not directed to the elected invention and species.

Claims 1-16 have been canceled.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5612185	UHR	03-1997
WO 97/27212	NOLAN	07-1997

Jia-ping, T., "Multi-parameter sorting technique in flow cytometry" Chinese Journal of Physical Medicine", Vol. 17, no.3, (September 1995), pp. 168-171.

Conneally, E., "Rapid and Efficient Selection of Human Hematopoietic Cells Expressing Murine Heat-Stable Antigen as an Indicator of Retroviral-Mediated Gene Transfer", Blood, vol. 87, no.2, (January 1996), pp. 456-464.

Hide, I. "Degranulation of individual Mast Cells in Response to Ca2+ and Guanine Nucleotides: An All-or-None Event", The Journal of Cell Biology, Vol. 123, Number 3. November 1993 585-593.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 USC 103 Rejection

Claims 17-24 and 30 are rejected under 35 U.S.C. 103(a) as being obvious over Uhr et al in view of Conneally et al.

Uhr discloses at e.g., col. 15, lines 35-50 a method of identifying(screening, as in claim 17) a candidate substance, e.g., antigen(candidate bioactive agents, as claim) capable of inducing cell cycle arrest in tumor cells (alteration in cellular phenotype, as claim) by contacting a population of tumor cells with the candidate substance, analyzing the population of tumor cells for the presence of cells which may be characterized as being under cell cycle arrest (cellular phenotype, as claim) by multiparameter cell sorting using fluorochromes that can be excited by 2 different lasers to give off light at 4 different wavelengths, possibly using 4 distinct antibodies to 4 different surface antigens and, in addition, using 2 light scattering parameters, direct and orthogonal. The cells can be separated on the basis of 6 parameters (step b, claim 7), preferably using fluorescence-activated flow cytometry (col. 3, lines 30-67). Uhr discloses at e.g., col. 4, line 61 up

to col. 6, line 65 the various methods employed to determine the DNA content of a cell cycle (cell cycle phenotype, as claim in the "wherein" clause) include, for example, any dye or binding material that indicates the amount of DNA per cell, such as the DNA-binding dye Hoechst 33342, propidium iodide or bromodeoxyuridine (BrdU). A further method for characterizing tumor cells as cells under cycle arrest is based upon the expression of certain key genes. The expression of genes which characterize arrested cells may be analyzed by any one of a variety of methods, including determining the levels of specific mRNA or protein (expression of a cell surface receptor and receptor protein, as claim). Protein levels may be analyzed by, for example, western blotting with specific antisera or by measuring the activity of the encoded protein by employing DNA gel shift assays or by analyzing the expression of genes known to be activated by such factors. The most straightforward and direct method of analyzing the expression of a particular gene is to measure the levels of the specific mRNA, which are known to those of skill in the art.

Uhr further discloses at e.g., FIG. I the flow cytometric identification of the population of cells analyzed for their light scatter profile, and their expression of Thy vs. λ and k

vs. λ performed on a FACScan. Forward light scattering, orthogonal light scattering, FITC and PE signals were determined for cells. The Hoechst 33342 staining is also used. The scatter and DNA profile of the gated cells are also shown. A cytometry software program was utilized that allows the simultaneous analysis of cell surface density of 4 MAb-defined antigens and two scatter parameters (forward and orthogonal). This simultaneous analysis enables a search for unique clusters of cells in six-dimensional space that is consistent with a dormant tumor cell population, i.e., a population that expresses appropriate antigens. Uhr discloses or contemplates at e.g., col. 22, lines 14-20 the preparation of vectors which incorporate nucleic acid sequences capable of encoding the desired genes introduced into the cells to be treated. The replication defective retrovirus may be used, as may other vectors. Uhr, alone, discloses or teaches all the elements of the claim method. Uhr does not positively teach library of retroviral vectors albeit, at least suggests said library of retroviral vectors. However, Conneally positively teaches at e.g., page 461, under the Discussion heading, the advantages in the use of recombinant retroviuses for the genetic modification of cells. One of the advantages is the ability to assess gene transfer to specific subpopulations of cells immediately after

infection. The detectable level is sorted by FACS. The use of recombinant retroviral vectors to transfect cells would have been obvious to one having ordinary skill in the art at the time the invention was made as taught by Conneally and at least contemplated by Uhr. The advantages provided by Conneally above would provide the motivation to use this recombinant virus. One having ordinary skill in the art would have a reasonable expectation of success in using retroviral vectors. These vectors have been conventionally use in the art and has been successfully employ in the art as taught by Conneally and at least suggested by Uhr, especially in transfecting mammalian cells.

Claims 17-25, 30 and 32 are rejected under 35 U.S.C. 103(a) as being obvious over Nolan in view of Jia-ping and Uhr et al.

Nolan et al discloses at e.g., page 31, line 1 up to page 32, line 6 a method comprising introducing a molecular library of randomized candidate nucleic acids into a plurality of cells, a cellular library. Each of the nucleic acids comprises a different, generally randomized, nucleotide sequence. The plurality of cells is then screened for a cell exhibiting an altered phenotype. The altered phenotype is due to the presence of a transdominant bioactive agent. Any phenotypic change may be

observed, detected, or measured on the basis of the screening methods. Suitable phenotypic changes include, but are not limited to gross physical changes such as changes in cell morphology, cell growth (cell cycle, as claim), cell viability (apoptosis, as claim), changes in the expression of one or more RNAs, proteins, changes in the localization of one or more RNAs, proteins, changes in the bioactivity or specific activity of one or more RNAs, proteins, changes in the secretion of ions, cytokines, hormones, growth factors, or other molecules and etc. The altered phenotype is detected in a wide variety of ways and will generally depend and correspond to the phenotype that is being changed. Generally, the changed phenotype is detected using, for example, Standard cell viability assays, including both increased cell death and increased cell viability, for example, cells that are now resistant to cell death via virus, bacteria, or bacterial or synthetic toxins; standard labeling assays such as fluorometric indicator assays for the presence or level of a particular cell or molecule, including FACS or other dye staining techniques; biochemical detection of the expression of target compounds after killing the cells. Once a cell with an altered phenotype is detected, the cell is isolated from the plurality which does not have altered phenotypes. This may be done in any number of ways, as is known in the art, and will in

some instances depend on the assay or screen. Suitable isolation techniques include, but are not limited to, FACS, scanning by Fluorimager, expression of a "survival" protein, induced expression of a cell surface protein or other molecule that can be rendered fluorescent or taggable for physical isolation; expression of an enzyme that changes a non-fluorescent molecule to a fluorescent one; death of cells and isolation of DNA or other cell vitality indicator dyes.

Nolan does not disclose a method in which the cellular phenotype is exocytosis and a 5-parameter cell sorting by FACS (although suggests said FACS analysis). However, Jia-ping discloses a method of sorting cells by multi-parameter sorting technique using flow cytometer including exocytosis. The method provides for an increased of purity of the divided cell and further information of the different cell subpopulations (page I).

Uhr is discussed above. It would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the changes in the exocytosis phenotype of a cell by at least 5 parameters in the method of Nolan in the manner as taught by Jia-ping and Uhr. One having ordinary skill in the art would have been motivated to sort the alteration in the phenotypic cells by at least 5 parameters based on

exocytosis phenotype of the cell for the advantages taught by Jia-ping and Uhr. The alteration in the exocytosis phenotype of the cell provides further information of the different cell subpopulations such that an increased purity of the divided cell is obtained. (The sorting of cells by FACS is known in the art as recognized by applicants' discussion of the BACKGROUND OF THE INVENTION at page 1, lines 25-28 of the instant disclosure).

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nolan in view of Jia-ping and Uhr et al as applied to claims 17-25, 30 and 32 above, and further in view of Hide et al and applicants' disclosure of known prior art.

Nolan is discussed above. Nolan discloses a FACS means of measuring the altered cellular phenotype but not exocytosis to measure annexin granule binding.

Hide discloses e.g., at page 588, col. 2 that cells contain large numbers of secretory granules which makes them highly refractile as manifested in the light-scattering properties of the cells, particularly at around 90 degrees. When the cells have undergone exocytosis, their refractivity is lost and their ability to scatter light at 90 degree is correspondingly diminished. This attribute has been used to classify populations of cells. Applicants at page 38, lines 10-20 admit that annexin is commercially available. It would have been obvious to one

having ordinary skill in the art at the time the invention was made to measure the cellular phenotype alteration in the method of Nolan by exocytosis using annexin granule binding as taught by Hide. Hide teaches that exocytosis measurement by granule binding is one of the means of classifying cell populations (and appears to be a sensitive measure of the cell behavior as shown by its high refractile property). Applicants admit in the instant disclosure that annexin is commercially available. One would have been motivated to use annexin because it is commercially available as admitted by appellants and because of the advantages in its use such as high sensitivity in detecting the phenotype exocytosis in cells as taught by Hide. There would be a reasonable expectation of success in the use of annexin as its effectiveness has been demonstrated by its commercial availability as successfully employed by Hide in his work.

(10) Response to Argument

Response to 35 USC 103 Rejection over Uhr

Appellants argue that Uhr does not teach or suggest a population of cells comprising a library of retroviral vectors. But recognize that Uhr (column 22) teaches that tumor cell cycle arrest may be induced by gene therapy and that a retrovirus may be used to introduce gene constructs. Appellants further argue that Uhr's Fig.3 and Example 2 relate to the expression of

oncogenes in tumor cells by assessing mRNA levels of c-myc and c-fos. These passages are unrelated to cells comprising a library of retroviral vectors. Appellants state that Conneally, like Uhr, fails to provide a library of retroviral vectors. Conneally teaches that a cell surface marker such as CD24 encoded by retroviral constructs can facilitate identification and selection of cells. Appellants state that this passage does not provide a library of retroviral vectors, as recited in claim 17. Appellants conclude that for each of the reasons set forth above, Uhr alone or in combination with Conneally does not teach or suggest each and every element of the rejected claims. Since Claim 17 is the only independent claim of this application, the arguments presented above apply with equal force to all other rejected claims.

In reply, attention is drawn to the disclosure of Uhr at e.g., col. 3, lines 50-55:

> Suitable techniques of multiparameter cell sorting will be known to those of skill in the art in light of the present disclosure. Generally speaking one contacts the **population of tumor cells to be analyzed with a panel** (another known art term for population or library) **of antibodies directed against distinct cell surface molecules**…. The antibodies …would be labeled in a manner to allow their subsequent detection, such as by tagging with a fluorescent label. By using fluorochromes that can be excited by 2 different lasers to give off light at 4 different wavelengths, it is possible to use 4 distinct antibodies to 4 different surface antigens and, in addition, to use 2 light scattering parameters, direct and orthogonal. Thus cells

> can be speared on the basis of 6 parameters. The population of tumor cells with bound antibodies may then be separated by cell sorting, preferably using fluorescence-activated flow cytometry.
> (Emphasis added).

Uhr further discloses at e.g., col. 22:

> …… DNA encoding key gene**s** such as, for example, c-fos or c-jun, may be **applied directly to cells, in the form of oligonucleotides, or other genetic constructs…..The preparation of vectors which incorporate nucleic acid sequences capable of encoding the desired genes, once introduced into the cells to be treated, is contemplated.**
> (Emphasis added).

The above teachings of Uhr that the panel of antibodies can be applied either directly to cells or in the form of other genetic constructs such as replication defective retrovirus (col. 22, lines 14-20) would lead one having ordinary skill in the art to the claim method.

Contrary to appellants' assertion, FIG. 3, cited by appellants above similarly discloses a library or panel of the three compounds comprising c-myc, c-fos and beta actin. Fig. 3 recites:

> …mRNA levels of c-myc, c-fos and .beta.-actin were quantified by PCR… Cells were isolated from the spleens by FACS as Thy1 and lambda…cDNA was synthesized from a mixture of 104 cell-equivalents of total RNA and 106 (myc and fos panels) or 107 (actin panel) OQ-1 synthetic RNA molecules by random priming.

Read in light of appellants' specification [paragraph [0047] of the published application 20030190684], a

"population of cells" or "library of cells" or "plurality of cells" [herein] is meant at least two cells.

The three compounds c-myc, c-fos and beta actin taught by Uhr falls in appellants' definition of a library above. (Please note that the instant Examples in the specification provide for only two compounds (cf. to at least three of Uhr) and not for a library of retroviral vectors encoding different bioactive agents as in claim 17.)

Conneally discloses also a retroviral library of two HSA compounds. At e.g., page 462, col. 2, Conneally discloses the major advantages of the (HSA/CD24) **family of vector** (another art term for a library).

Appellants state that "[a] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. See also e.g., KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1740 (2007

In reply, Uhr's disclosure, or at least suggestion, of a library of retroviral constructs is obvious because the elements comprised therein are found in a single prior art (Uhr). The combination of the known elements in the single prior art (Uhr) functions in a similar manner as that claim. When considering obviousness of a combination of known elements, the operative

question is thus "whether the improvement is more than the predictable use of prior art elements according to their **established functions.**" KSR International Co. v. Teleflex Inc., 550 USPQ2d 1385 (2007). (Emphasis added).

There is nothing new and unobvious in transfecting a library of cells with a library of vectors (retroviral) containing different candidate compounds to screen for said compounds that affect changes in a cell. Such technique has long been used in the recombinant art of screening candidate compounds. Appellants' instant specification at e.g., paragraph [0089] recognizes this known method by referring to the use of retroviral vectors as generally outlined in PCT US97/01019 and PCT US97/01048).

The actual application of the known screening technique in the art using known elements as a library of retroviral vectors is not beyond the skill of one of ordinary skill in the art rather, is routine in the art.

Response to 35 USC rejection over NOLAN

Appellants state that the following arguments are directed to all claims. Appellants submit that Nolan cannot preclude the patentability of the rejected claims. Appellants' state that the instant application's earliest priority date is April 17, 1998, as indicated on the filing receipt and the application data

sheet of this application. The relevant section of the filing receipt is reproduced below for the Board's convenience.

Domestic Priority data as claimed by applicant

This application is a CIP of 09/157,748 09/21/1998 PAT 6,461,813 which is a CIP of 09/062,330 04/17/1998 PAT 6,897,031. Appellants therefore urge that Nolan's publication date (July 31, 1997) predates the earliest priority date of this application (April 17, 1997) (sic, 1998) by less than a year. As such, Nolan only qualifies as prior art only under 35 U.S.C. § 102(a). Appellants state that a Declaration under 35 U.S.C. § 1.131 (the "Fisher Declaration"; submitted herein in the Evidence Appendix of this brief) was submitted with the Appellants' response dated July 24, 2006, in order to obviate a rejection over a similar combination of references (i.e., Nolan in view of Jai-ping or Ryan). The Fisher Declaration establishes invention of the subject matter of the rejected claims prior to the Nolan's publication date and, as such, Nolan cannot preclude the patentability of the instant claims. Since Nolan was published on July 31, 1997, Nolan was published less than one year before the Appellants' earliest priority date. As such, the Examiner's position, i.e., that "Nolan was published more than one year of applicants' earliest filing date" lacks support.

In response, Nolan was published more than one year of applicants' earliest filing date (please note appellants' statement that the instant application is a continuation-in-part (CIP) of the 09/062,330 application). The 09/062330(now US Patent 6,897,031)('031 Patent) does not provide support for the present broad claim "at least 5 parameters" as applied to the different claim cellular phenotypes. The different claim phenotypes consist of cell cycle, apoptosis, exocytosis, expression of a cell surface receptor, and expression of a receptor protein. The '031 Patent provides only four (4) parameters solely for exocytosis. It does not provide support for the other claim cell phenotypes having "at least five (5)" parameters being determined. See e.g., Example 9 of the '031 Patent. Thus, appellants are not entitled to the priority date of the '330 application ('031 Patent).

The Fisher declaration under 35 U.S.C. § 1.131 does not overcome the 35 USC 103 rejection as the declaration has no effect on a 35 USC 103 based on 35 USC 102(b) rejection. Nonetheless, for the sake of arguments, the Fisher declaration, Exhibits A-C, does not overcome the rejection for the following reasons:

Exhibit A is limited to FACS parameter measurement of the exocytosis phenotype (for which appellants were already granted

the '031 Patent above). The instant claim is not limited to the phenotype exocytosis but to the other phenotypes with broadly at least 5 parameters measured by FACS.

Exhibit B, as declarant states, was done after the Nolan's publication date of July 7, 1997 i.e., August 22-27. Like Exhibit A, Exhibit B shows result for exocytosis and not for the other claim cell phenotypes to which at least 5 parameters using FACS is determined. There is no showing of the "at least 5 FACS parameters" for each of the different claim cell phenotypes e.g., the phenotype expression of cell surface receptor or protein.

Exhibit C, uses staurosporine. There is no support of staurosporine in the as-filed disclosure of the '330 application or in the present specification.

Appellants rely on the foregoing arguments for the 35 USC 103 rejection of claim 26. Appellants submit that Nolan cannot be used as prior art under 35 U.S.C. § 103(a) because the subject invention predates the publication date of Nolan.

In reply, for the same reasons stated above, Nolan is a proper prior art under 35 USC 103 based on 102(b) rejection. For the reasons stated above appellants are not entitled to the priority date of their earliest application, the '330 application.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/TERESA WESSENDORF/

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